

WHAT IS CLAIMED IS:

- 1 1. A method of controlling cancer suppression in a mammal having a
2 cancer suppressing gene, comprising the steps of:
 - 3 making a substantially duplicated genetic material corresponding to the
4 genetic material of said gene, the substantially duplicated material selected from the group
5 consisting of a cloned cancer suppressing gene, a modified or defective cancer suppressing
6 gene, homologues thereof, fragments thereof, and mixtures thereof; and
7 interchanging said duplicated genetic material and the cancer suppressing gene
8 of the mammal.
- 1 2. A method of claim 1, wherein before said making a substantially
2 duplicated genetic material, determining the chromosomal location of said cancer suppressing
3 gene of the mammal.
- 1 3. A method of claim 1, wherein after said making a substantially
2 duplicated genetic material, detecting the presence or absence of an inactive cancer
3 suppressing gene of a tissue sample of the mammal to determine whether or not the tissue
4 sample cancer suppressing gene is defective or absent.
- 1 4. A method of claim 3, wherein in response to a determination that the
2 tissue sample cancer suppressing gene is either defective or absent, replacing a cancer
3 suppressing gene of the mammal with its clone.
- 1 5. A method of claim 3, wherein the determination of whether or not the
2 tissue sample cancer suppressing gene is defective or absent is accomplished by measuring
3 the amount of protein product of said cancer suppressing gene, of the tissue sample, bound by
4 an antibody specific for said protein.
- 1 6. A method of claim 5, wherein the determination of whether or not the
2 tissue sample cancer suppressing gene is defective or absent is accomplished by:
 - 3 (a) labeling said tissue sample with radioactive isotope;
 - 4 (b) lysing the labeled tissue;
 - 5 (c) reacting the protein product of said cancer suppressing gene with an
6 antibody specific for said protein thereby forming a protein/antibody immunocomplex;
 - 7 (d) autoradiographing the immunocomplex obtained in step (c); and

1 7. The method of claim 5, wherein the determination of whether or not
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by enzyme
3 immunoassay techniques.

1 8. The method of claim 5, wherein the determination of whether or not
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by
3 immunocytochemistry methods.

1 9. The method of claim 5, wherein the cancer suppressing gene is the RB
2 gene and the protein product is ppRB¹¹⁰.

1 10. The method of claim 1, wherein said cancer suppressing gene is
2 replaced with substantially duplicated material selected from the group consisting of said
3 cloned cancer suppressing gene, homologues thereof, fragments thereof, and mixtures
4 thereof, for therapeutic purposes.

1 11. The method of claim 1, wherein said cancer suppressing gene is
2 replaced with substantially duplicated material selected from the group consisting of said
3 defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures
4 thereof, for facilitating the testing of the carcinogenicity of environmental influences.

1 12. The method of claim 2, wherein the location of said cancer suppressing
2 gene is determined by chromosome walking.

1 13. The method of claim 2, wherein the location of said cancer suppressing
2 gene is determined through organic markers.

1 14. A method of claim 2, wherein:
2 said chromosomal location of said cancer suppressing gene is determined by
3 testing genes of a chromosome for phenotypic expression;
4 determining one of the genes of said chromosome to be a marker gene; and
5 using chromosomal walking techniques to locate a cancer suppressing gene.

1 15. An animal genetically altered so as to have the allele of at least one
2 cancer suppressing gene selected from the group consisting of a defective allele, a homologue
3 thereof, a fragment thereof, and a mixture thereof.

16. An animal of claim 15, wherein said defective allele is selected from
the group consisting of defective alleles of RB genes, breast cancer suppressing genes,
Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,
bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,
small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,
acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homologues
thereof, fragments thereof, and mixtures thereof.

1 17. An animal of claim 15, wherein said allele contains a DNA fragment
2 having at least one defective nucleotide sequence.

1 18. An animal of claim 15, wherein said defective allele contains a DNA
2 fragment having at least one defective RB nucleotide sequence.

19. The animal of claim 15, wherein said animal is a mouse.

1 20. A method for determining the carcinogenicity of suspected
2 environmental influences, using the animal of claim 14, comprising the steps of:
3 exposing said animal to a suspected environmental influence;
4 observing the animal for the phenotypic expression of cancer; and
5 determining carcinogenicity of the suspected environmental influence in
6 response to observing a phenotypic expression of cancer in the animal.

1 21. A method of claim 20, wherein said exposing includes exposing to a
2 source of radiation.

1 22. A method of claim 20, wherein said exposing includes exposing to
2 tobacco combustion products.

1 23. A method of claim 20, wherein said exposing includes exposing to
2 food additives.

1 24. A method of claim 20, wherein said exposing includes exposing to
2 artificial substances.

1 25. A method of claim 20, wherein said observing includes examining the
2 animal for tumor development.

1 26. A method of claim 25, wherein in response to the formation of a tumor
2 in the animal, analyzing the tumor for the presence of cancer cells.

1 27. A method of making the animal of claim 15, comprising:
2 using at least one allele of an animal cancer suppressing gene selected from
3 the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a
4 mixture thereof;
5 mutating at least one animal cell with said allele to form a mutated cell;
6 introducing said mutated cell into an animal blastocyst;
7 permitting growth of the blastocyst for a given period of time sufficient to
8 incorporate said allele into its cells; repressing genetic recombinations within said cells;
9 transferring the blastocyst containing said allele into the uterus of a pseudo pregnant animal
10 for giving birth subsequently to an animal bearing said allele;
11 breeding said animal to reproduce additional animals; and
12 selecting the animal of claim 14 from said additional animals by determining
13 the presence therein of the said allele.

1 28. A method of claim 27, wherein before introducing said allele,
2 removing said blastocyst from a super ovulated animal, and wherein said blastocyst is
3 comprised of undifferentiated cells.

1 29. A method of claim 27, wherein said introducing is performed in vitro.

1 30. A pharmaceutical composition wherein the active ingredient is selected
2 from the group consisting of a naturally occurring intact cancer suppressing gene, a cloned
3 intact cancer suppressing gene, fragments thereof, homologues thereof and mixtures thereof.

1 31. A pharmaceutical composition of claim 30, wherein said naturally
2 occurring and cloned cancer suppressing gene is selected from the group consisting of RB
3 genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-

4 Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing
 5 genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal
 6 cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma
 7 suppressing genes, homologues thereof, fragments thereof, and mixtures thereof.

1 32. A pharmaceutical composition of claim 30, wherein the active
 2 ingredient is selected from the group consisting of RB cDNA, modified RB cDNA fragment,
 3 clones thereof, homologues thereof and mixtures thereof.

1 33. A pharmaceutical composition of claim 31, wherein the active
 2 ingredient for each of said gene is selected from the group consisting of cDNA of said gene,
 3 fragments of said cDNA, homologues thereof and mixtures thereof.

1 34. A pharmaceutical composition of claim 32, wherein the cancer
 2 suppressing gene is isolated from human chromosome 13 region 13q14.

1 35. A pharmaceutical composition of claim 31, wherein the cancer
 2 suppressing gene and its clone each has the following nucleotide sequence:

4	TTCCGGTTTT	TCTCAGGGGA	CGTTGAAATT	ATTTTGTA	CGGGAGTCGG	GAGAGGACGG	60		
5	GGCGTCCCC	CGTGC	CGC	CGTCGTCCT	CCCCGGCGCT	CCTCCACAGC	TCGCTGGCTC	120	
6	CCGCCGCGGA	AAGGC	GTC	ATG CCG CCC	AAA ACC CCC	CGA AAA ACG	GCC GCC	171	
7	Met	Pro	Pro	Lys Thr	Pro Arg	Lys Thr	Ala Ala		
8	10								
9	ACC GCC	GCC GCT	GCC GCG	GAA CCC	CCG GCA	CCG CCG	CCG CCC	219	
10	Thr Ala	Ala Ala	Ala Ala	Ala Ala	Glu Pro	Pro Ala	Pro Pro	Pro Pro	
11	15	20	25						
12	ACC GCG	TAG GAG	GAC CCA	GAG CAG	GAC AGC	GGC CCG	GAG GAC	CTG CCT	267
13	Pro Pro	Glu Glu	Asp Pro	Glu Glu	Gln Asp	Ser Gly	Pro Glu	Asp Leu	Pro
14	15	20	25						
15	30	35	40						
16	CTC GTC	AGG CTT	GAG TTT	GAA GAA	ACA GAA	GAA CCT	GAT TTT	ACT GCA	315
17	Leu Val	Arg Leu	Glu Phe	Glu Glu	Thr Glu	Glu Pro	Asp Phe	Thr Ala	
18	45	50	55						
19	60	65	70						
20	TTA TGT	CAG AAA	TTA AAG	ATA CCA	GAT CAT	GTC AGA	GAG AGA	GCT TGG	363
21	Leu Cys	Gln Lys	Leu Lys	Ile Pro	Asp His	Val Arg	Glu Arg	Ala Trp	
22	60	65	70						
23	80	85	90						
24	TTA ACT	TGG GAG	AAA GTT	TCA TCT	GTG GAT	GGA GTA	TTG GGA	GGT TAT	411
25	Leu Thr	Trp Trp	Glu Lys	Val Ser	Ser Ser	Val Asp	Gly Val	Leu Gly	Tyr
26	80	85	90						
27									
28									
29									
30									
31									
32									

33	ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA	459
34	Ile Gln Lys Lys Lys Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Ala	
35	95 100 105	
36		
37	GTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC	507
38	Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn	
39	110 115 120	
40		
41	ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT	555
42	Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp	
43	125 130 135	
44		
45	ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT	603
46	Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr	
47	140 145 150 155	
48		
49	GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT	651
50	Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu	
51	160 165 170	
52		
53	ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT	699
54	Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser	
55	175 180 185	
56		
57	GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG	747
58	Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly	
59	190 195 200	
60		
61	GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG	795
62	Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met	
63	205 210 215	
64	CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC	843
65	Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu	
66	220 225 230 235	
67		
68	AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA	891
69	Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg	
70	240 245 250	
71		
72	ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA	939
73	Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu	
74	255 260 265	
75		
76	GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT	987
77	Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys	
78	270 275 280	
79		
80	AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT	1035
81	Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe	
82	285 290 295	
83		
84	ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA	1083
85	Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu	
86	300 305 310 315	
87		
88	AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA	1131
89	Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu	
90	320 325 330	
91		
92	GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT	1179
93	Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser	

94	335	340	345	
95				
96	ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT			1227
97	Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp			
98	350	355	360	
99				
100	GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG			1275
101	Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met			
102	365	370	375	
103				
104	AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA			1323
105	Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln			
106	380	385	390	395
107				
108	CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA			1371
109	Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro			
110	400	405	410	
111				
112	AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC TTT AAA			1419
113	Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys			
114	415	420	425	
115				
116	GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA			1467
117	Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser			
118	430	435	440	
119				
120	CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC			1515
121	Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser			
122	445	450	455	
123				
124	ATG CTT AAA TCA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA			1563
125	Met Leu Lys Ser Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys			
126	460	465	470	475
127				
128	CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT			1611
129	Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu			
130	480	485	490	
131				
132	GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT			1659
133	Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp			
134	495	500	505	
135				
136	TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA			1707
137	Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu			
138	510	515	520	
139				
140	AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA			1755
141	Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu			
142	525	530	535	
143				
144	GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT			1803
145	Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His			
146	540	545	550	555
147				
148	CGA ATC ATG GAA TCC CTT GCA TGG CTC TCA GAT TCA CCT TTA TTT GAT			1851
149	Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp			
150	560	565	570	
151				
152	CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA			1899
153	Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu			
154	575	580	585	

155
 156 TCT GCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA 1947
 157 Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala
 158 590 595 600
 159
 160 GAT ATG TAT CTT CCT GTA AGA TCT CCA AAG AAA AAA GGT TCA ACT 1995
 161 Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Lys Gly Ser Thr
 162 605 610 615
 163
 164 ACG CGT GTA AAT TCT ACT GCA AAT GCA GAG ACA CAA GCA ACC TCA GCC 2043
 165 Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala
 166 620 625 630 635
 167
 168 TTC CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTG TTT TAT 2091
 169 Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr
 170 640 645 650
 171
 172 AAA AAA GTG TAT CGG CTA GCC TAT CTC CGG CTA AAT ACA CTT TGT GAA 2139
 173 Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu
 174 655 660 665
 175
 176 CGC CTT CTG TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT 2187
 177 Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu
 178 670 675 680
 179
 180 TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT 2235
 181 Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His
 182 685 690 695
 183
 184 TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG 2283
 185 Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys
 186 700 705 710 715
 187
 188 AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT 2331
 189 Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu
 190 720 725 730
 191
 192 CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG 2379
 193 Pro His Ala Val Gln Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu
 194 735 740 745
 195
 196 GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA 2427
 197 Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg
 198 750 755 760
 199
 200 CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG 2475
 201 Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu
 202 765 770 775
 203
 204 TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA 2523
 205 Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser
 206 780 785 790 795
 207
 208 CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG AAG AGT 2571
 209 Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser
 210 800 805 810
 211
 212 CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA 2619
 213 Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro
 214 815 820 825
 215

216	AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG	2667
217	Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu	
218	830	835
219		840
220	AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC	2715
221	Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	
222	845	850
223		855
224	AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA	2763
225	Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu	
226	860	865
227		870
228	875	
229	CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC	2811
230	Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu	
231	880	885
232		890
233	CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT	2859
234	Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr	
235	895	900
236		905
237	CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	2907
238	Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
239	910	915
240		920
241	AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT	2962
242	Asn Lys Glu Glu Lys	
243	925	
244	GGATTCAATTG TCTCTCACAG ATGTGACTGT AT	2994

1 36. A pharmaceutical composition of claim 32, wherein said RB cDNA
 2 fragment is selected from the group consisting of RB-1, RB-2, RB-5, γ 79R8 and mixtures
 3 thereof.

1 37. A pharmaceutical composition of claim 32, wherein a resulting mRNA
 2 transcript of said RB cDNA fragment has 4.6 kb.

1 38. A pharmaceutical composition of claim 37, wherein the cloned
 2 genomic DNA has at least 27 exons.

1 39. A pharmaceutical composition of claim 30, wherein the cloned RB
 2 cDNA transcribes into mRNA which translates in protein having an amino acid sequence
 3 comprising:

4 **M**PPKTPRKTAATAAAAAEPPAPPPPPPEEDPE (34)
 5 QDSGPEDLPLVRLFEETEEDFTALCQKLKIPDHVRERA (74)
 6 WLTWEKVSSVDGVLGGYIQKKKELWGICIFIAAVDLDEM (114)
 7 FTFTELQKNIEISVHKFFNLLKEIDTSTKVDNAMSRLLKK (154)
 8 YDVLFALFSKLERTCLEIYLTPSSSISTEINSALVLKVS (194)
 9 WITFLLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML (234)
 10 LKEPYKTAVIPINGSRTPRRGQMRSARIAKQLENDTRII (274)
 11 EVLCKEHECNIDEVKNVYFKNFI PFMNSLGLVTSNGLPEV (314)
 12 ENLSKRYEEIYLKNKDLDARLFLDHDKTLQTDISFETQ (354)
 13 RTPRKSNLDEEVNVIPHTPVRTVMNTIQQLMMILNSASD (394)
 14 QPSENLISYFNNCTVNPKESILKRVKDIGYIFKEKFAKAV (434)
 15 GQGCVEIGSQRYKLGVRLYYRVMESMLKSEEERLSIQNFS (474)
 16 KLLNDNIFHMSLLACALEVVVMATYSRSTSQNLDGTDLSF (514)
 17 PWILNVNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE (554)
 18 HRIMESLAWLSDSPLFDLICKQSKDREGPTDHLESACPLNL (594)
 19 PLQNNHTAADMYLSPVRSPKKKGSTTRVNSTANAETQATS (634)
 20 AFQTQKPLKSTSLSLFYKKVYRLAYRLNTLCERLLSEHP (674)
 21 ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV (714)
 22 KNIDLKFKIIVTAYKDLPHAVQETFKRVLIKEEYDSIIV (754)
 23 FYNNSVFMQRLKTNILQYASTRPTLSPIPHI PRSPYKFPS (794)
 24 SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRILVS (834)
 25 IGESFGTSEKFQKINQMVCNSDRVLRSAEGSNPPKPLKK (874)
 26 LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ (914)
 27 KMNDSDMTSNKEEK (928)
 28
 29
 30 single-letter abbreviations for the amino acid residues are:
 31 A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His;
 32 I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln;
 33 R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

1 40. A DNA nucleotide sequence comprising:

2
 3 TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTGTA CGGGAGTCGG GAGAGGACGG 60
 4
 5 GCGTGCCTCC GCGTCGCGC GCGTCGTCCT CCCCCGGCGCT CCTCCACAGC TCGCTGGCTC 120
 6
 7 CCGCCGCGGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC 171
 8 Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala
 9 1 5 10
 10
 11 ACC GCC GCC GCT GCC GCG GAA CCC CCG GCA CCG CCG CCG CCG CCC 219
 12 Thr Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro
 13 15 20 25
 14
 15 CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GAC CTG CCT 267
 16 Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro
 17 30 35 40
 18
 19 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA 315
 20 Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala
 21 45 50 55
 22
 23 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG 363

24	Leu	Cys	Gln	Lys	Leu	Lys	Ile	Pro	Asp	His	Val	Arg	Glu	Arg	Ala	Trp	
25	60				65						70					75	
26																	
27	TTA	ACT	TGG	GAG	AAA	GTT	TCA	TCT	GTG	GAT	GGA	GTA	TTG	GGA	GGT	TAT	411
28	Leu	Thr	Trp	Glu	Lys	Val	Ser	Ser	Val	Asp	Gly	Val	Leu	Gly	Gly	Tyr	
29						80				85					90		
30																	
31	ATT	CAA	AAG	AAA	AAG	GAA	CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA	459
32	Ile	Gln	Lys	Lys	Glu	Leu	Trp	Gly	Ile	Cys	Ile	Phe	Ile	Ala	Ala		
33						95				100					105		
34																	
35	GTT	GAC	CTA	GAT	GAG	ATG	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC	507
36	Val	Asp	Leu	Asp	Glu	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lys	Asn	
37						110			115						120		
38																	
39	ATA	GAA	ATC	AGT	GTC	CAT	AAA	TTC	TTT	AAC	TTA	CTA	AAA	GAA	ATT	GAT	555
40	Ile	Glu	Ile	Ser	Val	His	Lys	Phe	Phe	Asn	Leu	Leu	Lys	Glu	Ile	Asp	
41						125			130						135		
42																	
43	ACC	AGT	ACC	AAA	GTT	GAT	AAT	GCT	ATG	TCA	AGA	CTG	TTG	AAG	AAG	TAT	603
44	Thr	Ser	Thr	Lys	Val	Asp	Asn	Ala	Met	Ser	Arg	Leu	Leu	Lys	Tyr		
45						140			145						150	155	
46																	
47	GAT	GTA	TTG	TTT	GCA	CTC	TTC	AGC	AAA	TTG	GAA	AGG	ACA	TGT	GAA	CTT	651
48	Asp	Val	Leu	Phe	Ala	Leu	Phe	Ser	Lys	Leu	Glu	Arg	Thr	Cys	Glu	Leu	
49						160			165						170		
50																	
51	ATA	TAT	TTG	ACA	CAA	CCC	AGC	AGT	TCG	ATA	TCT	ACT	GAA	ATA	AAT	TCT	699
52	Ile	Tyr	Leu	Thr	Gln	Pro	Ser	Ser	Ser	Ile	Ser	Thr	Glu	Ile	Asn	Ser	
53						175			180						185		
54																	
55	GCA	TTG	GTG	CTA	AAA	GTT	TCT	TGG	ATC	ACA	TTT	TTA	TTA	GCT	AAA	GGG	747
56	Ala	Leu	Val	Leu	Lys	Val	Ser	Trp	Ile	Thr	Phe	Leu	Leu	Ala	Lys	Gly	
57						190			195						200		
58																	
59	GAA	GTA	TTA	CAA	ATG	GAA	GAT	GAT	CTG	GTG	ATT	TCA	TTT	CAG	TTA	ATG	795
60	Glu	Val	Leu	Gln	Met	Glu	Asp	Asp	Leu	Val	Ile	Ser	Phe	Gln	Leu	Met	
61		205				210					215						
62	CTA	TGT	GTC	CTT	GAC	TAT	TTT	ATT	AAA	CTC	TCA	CCT	CCC	ATG	TTG	CTC	843
63	Leu	Cys	Val	Leu	Asp	Tyr	Phe	Ile	Lys	Leu	Ser	Pro	Pro	Met	Leu	Leu	
64		220			225					230					235		
65																	
66	AAA	GAA	CCA	TAT	AAA	ACA	GCT	GTT	ATA	CCC	ATT	AAT	GGT	TCA	CCT	CGA	891
67	Lys	Glu	Pro	Tyr	Lys	Thr	Ala	Val	Ile	Pro	Ile	Asn	Gly	Ser	Pro	Arg	
68						240			245						250		
69																	
70	ACA	CCC	AGG	CGA	GGT	CAG	AAC	AGG	AGT	GCA	CGG	ATA	GCA	AAA	CAA	CTA	939
71	Thr	Pro	Arg	Arg	Gly	Gln	Asn	Arg	Ser	Ala	Arg	Ile	Ala	Lys	Gln	Leu	
72						255			260						265		
73																	
74	GAA	AAT	GAT	ACA	AGA	ATT	ATT	GAA	GTT	CTC	TGT	AAA	GAA	CAT	GAA	TGT	987
75	Glu	Asn	Asp	Thr	Arg	Ile	Ile	Glu	Val	Leu	Cys	Lys	Glu	His	Glu	Cys	
76		270			275					280							
77																	
78	AAT	ATA	GAT	GAG	GTG	AAA	AAT	GTT	TAT	TTC	AAA	AAT	TTT	ATA	CCT	TTT	1035
79	Asn	Ile	Asp	Glu	Val	Lys	Asn	Val	Tyr	Phe	Lys	Asn	Phe	Ile	Pro	Phe	
80		285			290					295							
81																	
82	ATG	AAT	TCT	CTT	GGA	CTT	GTA	ACA	TCT	AAT	GGA	CTT	CCA	GAG	GTT	GAA	1083
83	Met	Asn	Ser	Leu	Gly	Leu	Val	Thr	Ser	Asn	Gly	Leu	Pro	Glu	Val	Glu	
84						300			305			310			315		

85
 86 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA 1131
 87 Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu
 88 320 325 330
 89
 90 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT 1179
 91 Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser
 92 335 340 345
 93
 94 ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT 1227
 95 Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp
 96 350 355 360
 97
 98 GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG 1275
 99 Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met
 100 365 370 375
 101
 102 AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA 1323
 103 Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln
 104 380 385 390 395
 105
 106 CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA 1371
 107 Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro
 108 400 405 410
 109
 110 AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC TTT AAA 1419
 111 Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys
 112 415 420 425
 113
 114 GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA 1467
 115 Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser
 116 430 435 440
 117
 118 CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC 1515
 119 Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser
 120 445 450 455
 121
 122 ATG CTT AAA TCA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA 1563
 123 Met Leu Lys Ser Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys
 124 460 465 470 475
 125
 126 CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT 1611
 127 Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu
 128 480 485 490
 129
 130 GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT 1659
 131 Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp
 132 495 500 505
 133
 134 TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA 1707
 135 Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu
 136 510 515 520
 137
 138 AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA 1755
 139 Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu
 140 525 530 535
 141
 142 GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT 1803
 143 Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His
 144 540 545 550 555
 145

146	CGA ATC ATG GAA TCC CTT GCA TGG CTC TCA GAT TCA CCT TTA TTT GAT	1851
147	Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp	
148	560 565 570	
149		
150	CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA	1899
151	Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu	
152	575 580 585	
153		
154	TCT GCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA	1947
155	Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala	
156	590 595 600	
157		
158	GAT ATG TAT CTT TCT CCT GTA AGA TCT CCA AAG AAA AAA GGT TCA ACT	1995
159	Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Lys Gly Ser Thr	
160	605 610 615	
161		
162	ACG CGT GTA AAT TCT ACT GCA AAT GCA GAG ACA CAA GCA ACC TCA GCC	2043
163	Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala	
164	620 625 630 635	
165		
166	TTC CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTG TTT TAT	2091
167	Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr	
168	640 645 650	
169		
170	AAA AAA GTG TAT CGG CTA GCC TAT CTC CGG CTA AAT ACA CTT TGT GAA	2139
171	Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu	
172	655 660 665	
173		
174	CGC CTT CTG TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT	2187
175	Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu	
176	670 675 680	
177		
178	TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT	2235
179	Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His	
180	685 690 695	
181		
182	TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG	2283
183	Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys	
184	700 705 710 715	
185		
186	AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT	2331
187	Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu	
188	720 725 730	
189		
190	CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG	2379
191	Pro His Ala Val Gln Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu	
192	735 740 745	
193		
194	GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA	2427
195	Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg	
196	750 755 760	
197		
198	CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG	2475
199	Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu	
200	765 770 775	
201		
202	TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA	2523
203	Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser	
204	780 785 790 795	
205		
206	CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG AAG AGT	2571

207 Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser
208 800 805 810
209
210 CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA 2619
211 Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro
212 815 820 825
213
214 AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG 2667
215 Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu
216 830 835 840
217
218 AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC 2715
219 Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu
220 845 850 855
221
222 AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA 2763
223 Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu
224 860 865 870 875
225
226 CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC 2811
227 Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu
228 880 885 890
229
230 CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT 2859
231 Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr
232 895 900 905
233
234 CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA 2907
235 Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser
236 910 915 920
237
238 AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT 2962
239 Asn Lys Glu Glu Lys
240 925
241
242 GGATTCATTG TCTCTCACAG ATGTGACTGT AT 2994

1 41. A method of therapeutically treating inactive, mutative or absent
2 cancer suppressing genes comprising:

3 treating said inactive, mutative or absent cancer suppressing genes with at
4 least a portion of intact cancer suppressing genes.

1 42. A method of claim 41, wherein said cancer suppressing genes are each
2 a substance selected from the groups consisting of RB genes, breast cancer suppressing
3 genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,
4 bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,
5 small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,
6 acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, and mixtures
7 thereof.

1 43. A method of claim 41, wherein said treating includes:

2 treating said inactive, mutative or absent cancer suppressing gene with a
3 substance selected from the group consisting of an RB gene, a portion of said gene, or a
4 mixture thereof.

1 44. A method of claim 43, wherein said portion is selected from the group
2 consisting of RB cDNA, RB cDNA fragment, homologues thereof and mixtures thereof.

1 45. The method of claim 41, wherein the intact cancer suppressing gene, or
2 portion thereof, is delivered to the site of a tumor by means of a retrovirus.

1 46. A method of claim 41, wherein the intact cancer suppressing gene, or a
2 portion thereof, is delivered to the site of a tumor by a liposome.

1 47. A method of claim 41, wherein the location of said cancer suppressing
2 gene is determined by utilizing a genetic marker.